

This listing of claims will replace all prior versions, and listings, of claims in the application.

**Listing of Claims:**

Claims 1 – 9 (Cancelled).

10. (Previously Presented) A nanoparticulate composition comprising:

- (a) beclomethasone dipropionate particles having an average particle size of less than about 1000 nm; and
- (b) at least one surface modifier.

11. (Previously Presented) The composition of claim 10, wherein the effective average particle size of the beclomethasone dipropionate particles is less than about 1000 nm, meaning that at least 90% of the particles have a particle size of less than about 1000 nm.

12. (Previously Presented) The composition of claim 10, wherein the effective average particle size of the beclomethasone dipropionate particles is less than about 400 nm, meaning that at least 90% of the particles have a particle size of less than about 400 nm.

13. (Previously Presented) The composition of claim 10, wherein the effective average particle size of the beclomethasone dipropionate particles is less than about 300 nm, meaning that at least 90% of the particles have a particle size of less than about 300 nm.

14. (Previously Presented) The composition of claim 10, wherein the effective average particle size of the beclomethasone dipropionate particles is less than about 100 nm, meaning that at least 90% of the particles have a particle size of less than about 100 nm.

15. (Previously Presented) The composition of any of claims 11-14, wherein at least 95% of the beclomethasone dipropionate particles have a particle size less than the effective average.

16. (Previously Presented) The composition of any of claims 11-14, wherein at least 99% of the beclomethasone dipropionate particles have a particle size less than the effective average.
17. (Previously Presented) The composition of claim 10, wherein the surface modifier is present in an amount of from about 0.1% to about 90%, by weight, based on the total combined weight of the beclomethasone dipropionate and surface modifier.
18. (Previously Presented) The composition of claim 10, wherein the surface modifier is present in an amount of from about 0.1% to about 75%, by weight, based on the total combined weight of the beclomethasone dipropionate and surface modifier.
19. (Previously Presented) The composition of claim 10, wherein the surface modifier is present in an amount of from about 20% to about 60%, by weight, based on the total combined weight of the beclomethasone dipropionate and surface modifier.
20. (Previously Presented) The composition of claim 10 formulated as an aqueous dispersion.
21. (Previously Presented) The composition of claim 10 formulated as a dispersion in a liquid media selected from the group consisting of aqueous salt solutions, safflower oil, and a solvent.
22. (Previously Presented) The composition of claim 21, wherein the solvent is selected from the group consisting of ethanol, t-butanol, hexane, and glycol.
23. (Previously Presented ) The composition of claim 10, formulated as a dry composition.
24. (Previously Presented) The composition of claim 10, comprising two or more surface modifiers.

25. (Previously Presented) The composition of claim 10, wherein the surface modifier is selected from the group consisting of nonionic and ionic surfactants.

26. (Previously Presented) The composition of claim 10, wherein the surface modifier is selected from the group consisting of gelatin, casein, lecithin, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxy propylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, tyloxapol, poloxamers, poloxamines, dextran, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonate, mixtures of sucrose stearate and sucrose distearate,  $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$ , decanoyl-N-methylglucamide, n-decyl- $\beta$ -D-glucopyranoside, n-decyl- $\beta$ -D-maltopyranoside, n-dodecyl- $\beta$ -D-glucopyranoside, n-dodecyl- $\beta$ -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- $\beta$ -D-glucopyranoside, n-heptyl- $\beta$ -D-thioglucoside, n-hexyl- $\beta$ -D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl- $\beta$ -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- $\beta$ -D-glucopyranoside, octyl- $\beta$ -D-thioglucopyranoside, p-isononylphenoxypoly(glycidol), dioctylsulfosuccinate (DOSS), glycerol, dodecyl trimethyl ammonium bromide, a charged phospholipid, the triblock copolymer B20-3800, and the triblock copolymer B20-5000.

27. (Previously Presented) The composition of claim 26, wherein the surface modifier is selected from the group consisting of block copolymers of ethylene oxide and propylene oxide, tetrafunctional block copolymer derived from sequential addition of propylene oxide and

ethylene oxide to ethylenediamine, a dioctyl ester of sodium sulfosuccinic acid, and dimyristoyl phosphatidyl glycerol.

28. (Previously Presented) The composition of claim 10, wherein the surface modifier is polyvinyl alcohol.

29. (Withdrawn) A method of making a nanoparticulate beclomethasone dipropionate composition comprising contacting particles of beclomethasone dipropionate with at least one surface stabilizer for a time and under conditions to reduce the average particle size of the beclomethasone dipropionate particles to less than about 1000 nm.

30. (Withdrawn) The method of claim 29, comprising:

- (a) dispersing particles of beclomethasone dipropionate in a liquid dispersion media in which the particles are poorly soluble; and
- (b) applying mechanical means in the presence of grinding media to reduce the average particle size of beclomethasone dipropionate to less than about 1000 nm,

wherein the beclomethasone dipropionate particles are reduced in size in the presence of at least one surface modifier, or wherein at least one surface modifier is added to the liquid dispersion media following particle size reduction of beclomethasone dipropionate.

31. (Withdrawn) The method of claim 30, wherein the mechanical means is a dispersion mill.

32. (Withdrawn) The method of claim 31, wherein the dispersion mill is selected from the group consisting of a ball mill, an attritor mill, a vibratory mill, and a media mill.

33. (Withdrawn) The method of claim 29 or 30, wherein the time required to reduce the particle size of beclomethasone dipropionate is from about 1 minute up to about 5 days.
34. (Withdrawn) The method of claim 29 or 30, wherein the beclomethasone dipropionate particles are reduced in size at an ambient temperature.
35. (Withdrawn) The method of claim 29 or 30, wherein the beclomethasone dipropionate particles are reduced in size at a less than about of less than about 40°C.
36. (Withdrawn) The method of claim 30, wherein the grinding media is spherical in shape and has an average particle size of from about 0.1 mm to about 3 mm.
37. (Withdrawn) The method of claim 36, wherein the grinding media has an average particle size of from 0.2 mm to about 2 mm.
38. (Withdrawn) The method of claim 37, wherein the grinding media has an average particle size of from 0.25 mm to about 1 mm.
39. (Withdrawn) The method of claim 37, wherein the grinding media has an average particle size of from 0.25 mm to about 1 mm.
40. (Withdrawn) The method of claim 30, wherein the grinding media is spherical in shape and has an average particle size of less than about 75 microns.
41. (Withdrawn) The method of claim 30, wherein the grinding media has a density greater than about 3 g/cm<sup>3</sup>.

42. (Withdrawn) The method of claim 30, wherein the grinding media comprises a compound selected from the group consisting of zirconium oxide, zirconium silicate, glass, stainless steel, titania, alumina, 95% ZrO<sub>2</sub> stabilized with yttrium, and polymeric resin grinding media.
43. (Withdrawn) The method of claim 42, wherein the grinding media comprises spherical particles consisting essentially of a polymeric resin.
44. (Withdrawn) The method of claim 42, wherein the grinding media comprises spherical particles comprising a core which is coated with a polymeric resin.
45. (Withdrawn) The method of claim 42, wherein the polymeric resin is selected from the group consisting of crosslinked polystyrenes, styrene copolymers, polycarbonates, polyacetals, vinyl chloride polymers, vinyl chloride copolymers, polyurethanes, polyamides, fluoropolymers, high density polyethylenes, polypropylenes, cellulose ethers, cellulose esters, polyhydroxymethacrylate, polyhydroxyethyl acrylate, and silicone containing polymers.
46. (Withdrawn) The method of claim 45, wherein the polymeric resin is selected from the group consisting of polystyrene crosslinked with divinylbenzene, poly(tetrafluoroethylenes), cellulose acetate, and polysiloxanes.
47. (Withdrawn) The method of claim 42, wherein the polymeric resin is biodegradable.
48. (Withdrawn) The method of claim 47, wherein the biodegradable polymer is selected from the group consisting of poly(lactides), poly(glycolide) copolymers of lactides, copolymers of glycolide, polyanhydrides, poly(hydroxyethyl methacrylate), poly(imino carbonates), poly(N-acylhydroxyproline)esters, poly(N-palmitoyl hydroxyproline) esters, ethylene-vinyl acetate

copolymers, poly(orthoesters), poly(caprolactones), and poly(phosphazenes).

49. (Withdrawn) The method of claim 42, wherein the polymeric resin has a density of from about 0.8 to about 3.0 g/cm<sup>3</sup>.

50. (Withdrawn) The method of claim 44, wherein the core material of the grinding media is selected from the group consisting of zirconium oxides, zirconium silicate, glass, stainless steel, titania, alumina, and ferrite.

51. (Withdrawn) The method of claim 44, wherein the core material of the grinding media has a density greater than about 2.5 g/cm<sup>3</sup>.

52. (Withdrawn) The method of claim 44, wherein the thickness of the polymeric resin coating on the core is from about 1 to about 500 microns.

53. (Withdrawn) The method of claim 44, wherein the thickness of the polymeric resin coating on the core is less than the diameter of the core.

54. (Withdrawn) The method of claim 30, comprising:

- (a) continuously introducing particles of beclomethasone dipropionate and rigid grinding media into a milling chamber,
- (b) contacting the beclomethasone dipropionate particles with the grinding media while in the chamber to reduce the particle size of the beclomethasone dipropionate particles;
- (c) continuously removing beclomethasone dipropionate particles and the grinding media from the milling chamber, and
- (d) separating the beclomethasone dipropionate particles from the grinding media.



55. (Withdrawn) The method of claim 30, comprising recirculating the beclomethasone dipropionate particles and the grinding media through the milling chamber.
56. (Withdrawn) The method of claim 30, comprising using grinding media having more than one particle size.
57. (Withdrawn) The method of claim 56, comprising at least two sizes of grinding media:
- (a) having a mean particle size between about 1 and 300 mm; and
  - (b) having a mean particle size between about 300 and 1000 mm.
58. (Withdrawn) The method of claim 29, wherein the effective average particle size of the beclomethasone dipropionate particles is selected from the group consisting of less than about 1000 nm, less than about 400 nm, less than about 300 nm, and less than about 100 nm, meaning that at least 90% of the particles have a particle size less than the effective average.
59. (Withdrawn) The method of claim 58, wherein at least 95% of the beclomethasone dipropionate particles have a particle size less than the effective average.
60. (Withdrawn) The method of claim 58, wherein at least 99% of the beclomethasone dipropionate particles have a particle size less than the effective average.
61. (Withdrawn) The method of claim 29, wherein the surface modifier is present in an amount selected from the group consisting of from about 0.1% to about 90%, about 0.1% to about 75%, and about 20% to about 60%, by weight, based on the total combined weight of the beclomethasone dipropionate and surface modifier.
62. (Withdrawn) The method of claim 29, utilizing two or more surface modifiers.



63. (Withdrawn) The method of claim 29, wherein the surface modifier is selected from the group consisting of nonionic and ionic surfactants.

64. (Withdrawn) The method of claim 29, wherein the surface modifier is selected from the group consisting of gelatin, casein, lecithin, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxy propylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, tyloxapol, poloxamers, poloxamines, dextran, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonate, mixtures of sucrose stearate and sucrose distearate,  $C_{18}H_{37}CH_2C(O)N(CH_3)-CH_2(CHOH)_4(CH_2OH)_2$ , decanoyl-N-methylglucamide, n-decyl- $\beta$ -D-glucopyranoside, n-decyl- $\beta$ -D-maltopyranoside, n-dodecyl- $\beta$ -D-glucopyranoside, n-dodecyl- $\beta$ -D-maltoside, heptanoyl-N-methylglucamide, n-heptyl- $\beta$ -D-glucopyranoside, n-heptyl- $\beta$ -D-thioglucoside, n-hexyl- $\beta$ -D-glucopyranoside, nonanoyl-N-methylglucamide, n-nonyl- $\beta$ -D-glucopyranoside, octanoyl-N-methylglucamide, n-octyl- $\beta$ -D-glucopyranoside, octyl- $\beta$ -D-thioglucopyranoside, p-isononylphenoxypoly(glycidol), dioctylsulfosuccinate (DOSS), glycerol, dodecyl trimethyl ammonium bromide, a charged phospholipid, the triblock copolymer B20-3800, and the triblock copolymer B20-5000.

65. (Withdrawn) The method of claim 64, wherein the surface modifier is selected from the group consisting of block copolymers of ethylene oxide and propylene oxide, tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine, a dioctyl ester of sodium sulfosuccinic acid, and dimyristoyl phosphatidyl glycerol.

66. (Withdrawn) The method of claim 29, wherein the surface modifier is polyvinyl alcohol.
67. (Withdrawn) A method of making a nanoparticulate beclomethasone dipropionate composition comprising
- (a) dissolving beclomethasone dipropionate in an aqueous base with stirring;
  - (b) adding the solution of beclomethasone dipropionate with stirring to a solution of one or more surface modifiers to form a clear solution;
  - (c) neutralizing the formulation from step (b) with stirring with an appropriate acid solution, and
  - (d) recovering particles of beclomethasone dipropionate having an average particle size of less than about 1000 nm.
68. (Withdrawn) The method of claim 67, further comprising removing any formed salt by dialysis or diafiltration.
69. (Withdrawn) The method of claim 67, further comprising concentrating the resulting beclomethasone dipropionate dispersion to a desired concentration of beclomethasone dipropionate.
70. (Withdrawn) The method of claim 67, wherein step (c) is carried out in semicontinuous, continuous batch, or continuous methods at constant flow rates of the reacting components.
71. (Withdrawn) The method of claim 67, further comprising dissolving a crystal growth modifier in step (a) with the beclomethasone dipropionate.

72. (Withdrawn) The method of claim 67, wherein the effective average particle size of the beclomethasone dipropionate particles is selected from the group consisting of less than about 1000 nm, less than about 400 nm, less than about 300 nm, and less than about 100 nm, meaning that at least 90% of the particles have a particle size less than the effective average.

73. (Withdrawn) The method of claim 72, wherein at least 95% of the beclomethasone dipropionate particles have a particle size less than the effective average.

74. (Withdrawn) The method of claim 72, wherein at least 99% of the beclomethasone dipropionate particles have a particle size less than the effective average.